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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/551,764

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EXAMINER

NIEBAUER, RONALD T

ART UNIT

PAPER NUMBER

1654

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/551,764	<b>Applicant(s)</b> KIM ET AL.	
	<b>Examiner</b> RONALD T. NIEBAUER	<b>Art Unit</b> 1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 28 March 2008.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-3,5,8,9 and 12 is/are pending in the application.
- 4a) Of the above claim(s) 12 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3,5,8-9 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)          | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

### **DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/28/08 has been entered.

Applicants amendments and arguments filed 3/28/08 are acknowledged and have been fully considered. Any rejection and/or objection not specifically addressed is herein withdrawn.

Claims 4,6-7,10-11 have been cancelled.

Claim 12 remains withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/14/07.

Claims 1-3,5,8-9 remain under consideration.

### ***Claim Objections***

Applicant is advised that should claim 1 be found allowable, claim 9 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). In the instant case, claim 9 states that the second PEG molecule is linear or branched. Since every PEG molecule is either

linear or branched (it is unknown what other possibilities there are), claim 9 does not add a new limitation as currently recited.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**Claims 1-3,5,8-9** are rejected under 35 U.S.C. 103(a) as being unpatentable over Finn et al. (WO 03/044056) and Braxton (US 5,766,897, cited previously).

Finn teach the chemical modification of the human growth hormone (hGH) via a water soluble polymer that enables reduced dose (abstract). Finn teach that the use of water soluble polymers for decreasing the clearance rate, improving stability, and abolishing antigenicity of therapeutic proteins (page 5 lines 7-25 for example). Finn refers to many examples (page 8 last

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paragraph – page 11) in which pegylated human growth hormone has been used. Finn teach that previous reports require the attachment of many PEGs which results in undesired product heterogeneity and that the invention of Finn includes chemically modified hGH with improved properties (page 11 lines 8-26).

Finn specifically teaches the use of PEG (claim 4) and that attachment can be at a variety of locations (claim 5). Finn teach the attachment of the PEG at the N-terminus and at lysine residues (page 7 lines 22-23; page 15 lines 34-35; page 18 lines 3-14, examples) as recited in claims 2 and 3 of the instant invention. Finn specifically teaches the use of PEG with a variety of chemistries (claim 19). Finn teach the use of aldehyde functional groups (claim 9,20, page 22 line 24-26, examples) as recited in claim 5 of the instant invention. Finn teach the use of succinimidyl propionate functional groups (page 9 line 28-31, example 6) and maleimides (claim 37, page 9 line 11-12) as recited in claim 8 of the instant invention.

Finn teach a range of molecular weights for the PEG molecule (claim 42). Finn teach examples (example 2 and example 4, page 33; Figure 8) using 30kDa and 40kDa PEG as recited for the second PEG molecule of the instant invention. Finn teach the used of a branched PEG (claim 43) as recited in claim 9 of the instant invention. Finn teach the use of PEG to generate polymeric hGH (page 23 lines 20-24) specifically by crosslinking the molecules via PEG.

Finn does not expressly teach in a single embodiment the use of a polypeptide homodimer linked by a first PEG and having a second PEG molecule bonded to each of the polypeptide molecules.

As discussed above, Finn specifically teaches the use of 30kDa and 40kDa PEG molecules bonded to hGH (examples 2 and 4) which show (Figure 8) improved stability. Further, Finn teach the use of PEG to generate polymeric hGH (page 23 lines 20-24) specifically by crosslinking the molecules via PEG. Since Finn teach crosslinking of hGH via PEG one would be motivated to use hGH crosslinked by PEG.

Like Finn, Braxton teach PEGylated proteins that have increased half-lives with the same level of biological activity of the unmodified protein (abstract). Braxton specifically teach that hGH (column 25 line 14, Table 1a column 12, example I column 46-47) is a specific protein in which PEGylation results in increased half-life. Braxton specifically teach dimeric proteins cross-linked by PEG (column 3 lines 61-63). Braxton specifically teach dimeric proteins using maleimido chemistry (column 13 lines 55-65). Braxton teach that the PEG molecule for the crosslinking is from about 200 to 20000 MW, preferably about 1000 to 8000 MW, more preferably from about 3250 to 5000 MW, and most preferably about 5000 MW (column 12 lines 48-54, see also Example F column 36) as recited for the first PEG of the instant invention. Braxton teaches that a lysine residue is typically reacted with PEG (column 2 line 12). Braxton further teaches that PEG can be attached at particular residues (column 12 line 49). Braxton teach that the residue could be naturally present in the protein or could be introduced by site-directed mutagenesis (column 13 line 64-66).

It has been recently held that “Neither §103's enactment nor *Graham's* analysis disturbed the Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art.” KSR v. Teleflex, 550 U.S. \_\_\_, 82 USPQ2d 1385, 1389 (2007). The KSR court stated that “a combination of familiar elements according to

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known methods is likely to be obvious when it does no more than yield predictable results.” KSR at 1389.

Furthermore, The KSR court concluded that "obvious to try" may be an appropriate test under 103. The Supreme Court stated in *KSR*

When there is motivation

"to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, \_\_\_, 82 USPQ2d 1385, 1397 (2007).

In the instant case, both references teach the goal of obtaining hGH with improved half-life and stability. Taken together, the references teach the claimed elements. One of skill in the art could have combined the elements as claimed by known methods and the combination would have yielded predictable results to one of ordinary skill at the time of the reference. In particular, one would have used the teaching of Finn and Braxton to obtain hGH crosslinked with PEG (i.e. first PEG) using the specific MWs of the crosslinker as taught by Braxton. Further one would have used the teaching of Finn to obtain the 2nd PEG using the specific MWs as taught by Finn. Taken together, the locations (N-terminal, lysine), functional groups (aldehyde, succinimidyl propionate) and PEG type (branched) are all taught in the prior art as discussed above and one skilled in the art would have tried the various combinations because a person has good reason to pursue the known options within his or her grasp. The combination of using both a PEG to form a dimer and additional PEGs for added stability flows logically from their having been individually taught in the prior art. Regarding the predictability in the art, Braxton teach PEGylated proteins that have increased half-lives with the same level of biological activity of the

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unmodified protein (abstract). Further, Finn refers to many examples (page 8 last paragraph – page 11) in which pegylated human growth hormone has been used. From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

### ***Response to Arguments 103 rejection***

It is noted that a new rejection citing a new reference and using one of the same references from the previous rejection is recited above. Applicants arguments will be considered to the extent that they apply to the current rejection and claim set.

Applicants argue that the references do not teach the elements of claim 1. Applicants argue that the references only teach overlapping ranges and that the references fail to teach a first and second PEG molecule. Applicants argue that there is no suggestion or motivation to modify the complex with reasonable expectation of success. Applicants argue that the claimed invention shows unexpected effects specifically test examples 5 and 6 and Table 4 and Figure 3.

Applicant's arguments filed 3/14/08 have been fully considered but they are not persuasive.

It is noted that the instant rejection and the previous rejection were both multiple reference 103 rejections, thus any single reference does not teach every element of any one claims. As discussed in detail above, Braxton teach that the PEG molecule for the crosslinking is from about 200 to 20000 MW, preferably about 1000 to 8000 MW, more preferably from about



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3250 to 5000 MW, and most preferably about 5000 MW (column 12 lines 48-54, see also Example F column 36) thus meeting the limitation of the first PEG of the instant invention. Finn teach a range of molecular weights for the PEG molecule (claim 42). Finn teach examples (example 2 and example 4, page 33; Figure 8) using 30kDa and 40kDa PEG as recited for the second PEG molecule of the instant invention. Therefore the ranges and specific and preferred embodiments of the prior art meet the MW limitations (compare MPEP section 2131.03).

Regarding applicants arguments about a lack of a suggestion or motivation, section 2143 of the MPEP states:

The Courts have made clear that the teaching, suggestion, or motivation test is flexible and an explicit suggestion to combine the prior art is not necessary. The motivation to combine may be implicit and may be found in the knowledge of one of ordinary skill in the art, or, in some cases, from the nature of the problem to be solved. *Id.* at 1366, 80 USPQ2d at 1649.

In the instant case, as discussed above, Finn specifically teaches the use of 30kDa and 40kDa PEG molecules bonded to hGH (examples 2 and 4) which show (Figure 8) improved stability. Further, Finn teach the use of PEG to generate polymeric hGH (page 23 lines 20-24) specifically by crosslinking the molecules via PEG. Since Finn teach crosslinking of hGH via PEG one would be motivated to use hGH crosslinked by PEG. Both references are drawn to improving the half-life and stability of hGH and the combination of using both a PEG to form a dimer and additional PEGs for added stability flows logically from their having been individually taught in the prior art.

Regarding applicants assertion that the claimed invention shows unexpected results, MPEP section 716.02(b) states that the burden is on the applicant to establish that the results are unexpected and significant. As discussed above, both Finn and Braxton and many references

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therein recognize the use of PEG to improve the half-life and stability of hGH. As such, one would expect PEGylated hGH to show improved half-life and stability.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RONALD T. NIEBAUER whose telephone number is (571)270-3059. The examiner can normally be reached on Monday-Thursday, 7:30am-5:00pm, alt. Friday, EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ronald T Niebauer/  
Examiner, Art Unit 1654

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/Anish Gupta/

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